IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Matthias SCHNABELRAUCH et al.

Serial No. 10/580,549

for: Bioabsorbable Composite Material

filed: April 03, 2007
Int. Filing Date: November 25, 2004 (PCT/EP2004/013388)
Priority: November 27, 2003

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Dr. Matthias Schnabelrauch, Am Burggarten 17, D-07745 Jena, a citizen of Germany, hereby declare:

- that I have a degree in **Chemistry** having studied at Friedrich Schiller University in Jena, Germany;

- that I received a Ph.D. in **Chemistry** at **Friedrich Schiller University** in **Jena**, **Germany**, in 1988;

- that subsequent to my Ph.D., I worked as scientist and postdoctoral fellow at the Institute of Organic Chemistry and Macromolecular Chemistry of the Friedrich Schiller University in Jena from 1988 to 1991, at the Institute of Organic Chemistry of the University of Zurich and the Laboratory of Organic Chemistry of the Swiss Federal Institute of Technology, both in Zurich, Switzerland from 1991 to 1993, and at the Hans Knoell Institute for Natural Product Research in Jena, Germany from 1994 to 1996;

- that I entered the employ of Innovent e.V. in 1996, where I was appointed head of the biomaterials department and am responsible for the research and development of biomaterials;

- that I am a member of numerous work and planning groups/associations such as GDCh (Society of German Chemists), ESB (European Society of Biomaterials), DGM (German Society of Material Science), DGBM (German Society of Biomaterials) etc.

- that I have authored or co-authored about **90** articles, including articles in the field of biomaterial sciences, such as:

A. Berg, F. Peters, M. Schnabelrauch: Biodegradable (meth)acrylate-based adhesives for surgical applications. In: *Biological Adhesive Systems - From Nature to Technical and Medical Application* (Eds.: J. von Byern, I. Grunwald), Springer, Wien, **2010**, 261-272.

C. Heiss, R. Kraus, F. Peters, W. Henn, M. Schnabelrauch, A. Berg, T. Pautzsch, J. Weisser, R. Schnettler: Development of a bioresorbable self-hardening bone adhesive based on a composite consisting of polylactide

methacrylates and β-tricalcium phosphate. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* **90B** (2009), 55-66.

M. Schnabelrauch, S. Vogt, Y. Larcher, I. Wilke: Biodegradable polymer networks based on oligolactide macromers: synthesis, properties and biomedical applications. *Biomolecular Engineering* **19** (2002), 295-298.

- that I am named as inventor on numerous applications/patents relating to biomaterials and my field of research and expertise is in this area of biomaterials, where I apply my scientific background in inorganic chemistry and material science.

I am the same Matthias Schnabelrauch who is named as first inventor of U.S. Ser. No. 10/580,549 ("the '549 application"), filed on April 3, 2007. I am familiar with the invention described in the '549 application and am familiar with its prosecution history, in particular, the final Office Action mailed on December 7, 2010.

I understand that the Examiner objects to the arrangement of the specification and to Claim 14 for allegedly failing to comply with the written description requirement under 35 U.S.C. 112, first paragraph. Specifically, the Examiner's rejection asserts that no clear definition for the term "proteinogenic growth factors" could be construed from the prior art. I do not agree with the Examiner's assertions.

In my opinion, one of ordinary skill in the art would be readily aware of growth factors, which are proteins (i.e. proteinogenic) and are conventionally used in biomaterials/ medical arts. According to my knowledge, growth factors have been increasingly used in the medical arts for at least the

last two decades. Most growth factor proteins are commercially available and their use in the medical field is common practice. One of ordinary skill, therefore, would be able to practice the claimed invention without undue experimentation in finding and testing growth factor proteins by simply employing appropriate commercially available growth factor proteins.

For these reasons, it is my opinion that the Examiner's written description requirement rejection should be reconsidered and withdrawn for pending Claim 14 in the '549 application.

I also understand that the Examiner rejected all pending claims, Claims 1, 2, 4-7, 9-29, 31 and 40-43 as allegedly being obvious over my prior art German patent DE 199 39 403 (DE '403), or further over a combination of DE '403 and Draenert (USPN 4,373,217).

Specifically, the Examiner's rejection asserts that one of ordinary skill in the field of biomaterials would have had a reasonably high expectation of arriving at and achieving the claimed method in view of the teachings, especially Examples 4-6, of the DE '403 patent. The Examiner further asserts that deficiencies of DE '403 are remedied by the teachings of Draenert. I respectfully submit that the Examiner's assertions are incorrect, for the reasons more fully described below.

Pending Claim 1 as reflected in the Amendment - after non-final rejection filed on September 23, 2010, reads as follows:

1. (Currently amended) Method of producing a self-hardening bioabsorbable composite material, wherein

(i) a polymerisation initiator is immobilised with the aid of a first partial amount of an interconnectingly porous bioabsorbable inorganic bone regeneration material,

(ii) a polymerisation activator is immobilised with the aid of a second partial amount of the bone regeneration material according to (i) or of a different interconnectingly porous bioabsorbable inorganic bone regeneration material,

(iii) the components obtained in steps (i) and (ii) are mixed with a liquid or paste-form multi-functional monomer capable of polymerisation to form a biocompatible and bioabsorbable polymer or with a liquid or paste-form mixture of multi-functional monomers capable of polymerisation to form a biocompatible and bioabsorbable polymer, wherein at least one of the constituents mixed in is a water-soluble pore-forming substance which is added to the monomer, monomer mixture and/or the mixture thereof with the bone regeneration material in particulate form, and

(iv) the monomer or monomer mixture contained in the mixture produced is polymerised and the composite material is obtained;

wherein

calcium phosphate having a pore volume, accessible to the polymerisation initiator and/or the polymerisation activator, of 0.4 cm^3/g or more, while retaining the integrity of the particles of the bone regeneration material and having the following characteristic data is used as the interconnectingly porous bioabsorbable inorganic bone regeneration material:

- pore diameters from 0.1 to 500 µm; and/or
- particle sizes (d_{50} values) of from 1 to 500 µm; and/or
- BET surface area of at least 0.1 m^2/g.

Since all other pending claims depend directly or indirectly on pending Claim 1, my arguments presented in response to Examiner's assertions will focus on the limitations of Claim 1.

I understand that the Examiner maintains the obviousness rejection because the Examiner believes that a skilled artisan would have had a reasonably high expectation of successfully arriving at the claimed invention and would also have been particularly motivated by the prior art teachings to modify them according to the claimed invention. I disagree.

Admittedly, bone cements comprising calcium phosphate are known since the 1970ties. Even porous cements have been described as taught by Draenert with reference to J. Biomed. Mater. Res. 11, 373-394 (1977) and other documents. However, as taught by Draenert, all of these bone cements have been found to lack the required stability (see, for example, Draenert, Col. 1, line 67 to Col. 2, line 10).

Moreover, Draenert also teaches that calcium phosphates possessing a large pore volume on the order of about 0.3-0.5 ml/g are normally relatively soft (Col. 3, lines 50-52) and show numerous disadvantages (Col. 3, line 58 to Col. 4, line 12). For instance, curing of the cement is no longer ensured due to incomplete polymerization of the acrylate or methacrylate monomers employed to form the cement. As a result, there is the danger that a relatively large proportion of residual acrylate or methacrylate monomer will remain after curing and pass into the patient's circulatory system. In addition, polymerization of the acrylate or methacrylate monomers in the pores significantly hampers resorbability of the calcium phosphate.

To avoid these disadvantages, both DE '403 and Draenert suggest to use "non-porous" bioabsorbable inorganic fillers.

As for DE '403, it should be noted that Examples 4-6 use calcium carbonate as inorganic filler as opposed to the calcium phosphate recited in Claim 1.

There is, moreover, no teaching or suggestion in DE '403 to employ a porous bioabsorbable inorganic filler, let alone the calcium phosphate having the features recited in Claim 1. On the contrary, DE '403 teaches that pores develop after resorption of the inorganic filler under in vivo conditions.

In addition, DE '403 teaches to coat the inorganic filler on its surface. In contrast, in the claimed invention the polymerisation initiator and/or polymerisation activator is completely drawn up into a pore system; see, for example, preparation of starting components A and B at page 17 of the instant specification.

Thus, DE '403 does not teach the claimed method and is also not readable upon or suggestive of the claimed method, since it fails to disclose the specific calcium phosphate recited in the claims. While calcium phosphate is mentioned in DE '403, this document is entirely silent with respect to the porous calcium phosphate claimed. Since the behavior of a cement is strongly dependent on the actual filler employed, a skilled artisan would have had no reason to conclude that a porous filler material would indeed be effective, especially in view of the known and widely recognized disadvantages of porous fillers.

These deficiencies are also not remedied by Draenert. Contrary to Examiner's assertions, Draenert does not teach a method with the steps recited in Claim 1 nor does he teach or suggest

the use of the claimed porous calcium phosphate having the features recited in Claim 1. In particular, *to exclude these complications caused by the prior art porous structure of the calcium phosphate employed* (Draenert, Col. 4, line 33-35; emphasis added), Draenert teaches to use a calcium phosphate having a pore volume of below 0.1 ml/g, preferably below 0.05 ml/g. This pore volume is achieved in that the precipitated tricalcium phosphate starting materials having a pore volume of 0.35 ml/g and 0.4 ml/g, respectively (see, Draenert Example 3a, and Col. 4, line 44-60) are annealed at elevated temperatures. Notably, Draenert (as opposed to the present invention) teaches to mix these annealed starting materials having a pore volume of below 0.1 ml/g with polymerisable monomers. In Example 1, Draenert teaches to fill the pores of the porous calcium phosphate with glycerin to thereby reduce the pore volume to less than 0.1 ml/g (cf. Col. 4, lines 18-32, especially lines 30-32).

Thus, Draenert clearly fails to teach or suggest the claimed method, which employs calcium phosphate having a pore volume of 0.4 cm^3/g or more (ml/g). In fact, not only is Draenert entirely silent with respect to a calcium phosphate having a pore volume of 0.4 cm^3/g or more, but he also teaches actively away from the claimed calcium phosphate in that he only teaches and suggests the use of pretreated tricalcium phosphate having a pore volume of less than 0.1 ml/g (see, Claims, Specification and Examples 1-4 of Draenert).

Moreover, Draenert relates to a bone cement that is not resorbed by the body. as opposed to the claimed bioabsorbable composite material. The differences between these implant materials are well known in the art, and therefore one of ordinary skill in the art would recognize that the Draenert reference would not be readable upon or suggestive of the claimed bioabsorbable composite material. In fact, Draenert is

directed toward an implantation material with a complete opposite mode of action to that of the instant invention. The Draenert reference is, therefore unrelated to the teaching of DE '403 or the claimed invention.

It is my firm opinion that there is no reason offered from either Draenert or DE '403 for making this combination and even a combination would not lead to the claimed invention, since there is no reason offered in the respective teachings of DE '403 or Draenert to select the use of the specific claimed calcium phosphate, as the necessary element to be modified; one of ordinary skill in the art could have tried any number of DE '403's other elements for modification (e.g. different preferred filler, different pore volume, different pore diameter, different particle size, different BET surface area, etc) such that rather than a finite number of solutions, there was an infinite number of solutions for a novel self-hardening bioabsorbable composite material that also realizes the advantages of non-porous materials (e.g. stability) despite its dramatically increased porosity.

For any of the above reasons, I do not agree with the Examiner's belief about the reasonable expectation of a skilled artisan in view of the state of the art. In my opinion, one of ordinary skill in the art would have had no reason to conclude that the claimed method, which (as opposed to the applied art) employs a specific, porous calcium phosphate, would result in a material that shows the required stability and readily resorbs, especially in view of the details Draenert supplies in describing the disadvantageous properties of conventional, porous tricalcium phosphates, namely lack of the required stability and extensive prevention of resorption (Col. 1 through Col. 4, line 6).

It is my position that the present invention, against all expectations, especially in the light of the applied prior art, surprisingly shows that it is possible to produce an effective and advantageous bioabsorbable material from a specific, porous calcium phosphate. Notably, the applied art nowhere teaches or suggests the specific claimed calcium phosphate and provides no apparent reason to specifically select the features recited in Claim 1 to arrive at the claimed combination.

In view of the remarks to the applied art presented herein, it is my opinion that the Examiner's written description and obviousness rejections should be reconsidered and withdrawn for all of the pending claims in the '549 application.

The undersigned further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and the foregoing statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 01/03/2011

By: _____

Matthias Schnabelrauch, Ph.D.